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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/063,596	05/03/2002	Audrey Goddard	P3230R1C001-168	2711

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EXAMINER	
WEGERT, SANDRA L	

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 01/09/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/063,596	GODDARD ET AL.	
	Examiner	Art Unit	
	Sandra Wegert	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on 9/29/06.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 4-17 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 4-17 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on 03 May 2002 is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 9/29/05.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Detailed Action

Status of Application, Amendments, and/or Claims

The Response, submitted 29 September 2005, has been entered. The Information Disclosure Statement, submitted 29 September 2005 has been entered. Claims 1-3 were cancelled previously by Applicant (8 April 2005).

Claims 4-17 are under examination in the Instant Application.

The text of those sections of Title 35, U.S. Code, not included in this action can be found in a prior Office action.

Maintained Objections and/or Rejections

35 U.S.C. § 101/112, first paragraph-, Lack of Utility, Enablement.

Claims 4-17 are rejected under 35 U.S.C. 101, as lacking utility. The reasons for this rejection under *35 U.S.C. § 101* are set forth at pp. 3-6 of the previous Office Action (28 June 2005). Claims 4-17 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth in the previous Office Action (28 June 2005), one skilled in the art clearly would not know how to use the claimed invention.

Applicants argue (29 September 2005, pages 7 and 8) that the results presented in the instant Specification are enabling for the polypeptide of SEQ ID NO: 90. They argue that PRO1268 message is differentially expressed in kidney tumor versus normal kidney, and point to

the results of the expression assay (pages 140-143, Specification). The assay indicated showed a 2-fold or greater fluorescence in samples of one kidney tumor tissue versus normal kidney tissue.

Applicant's arguments (29 September 2005) have been fully considered but are not found to be persuasive for the following reasons:

In the instant case, the specification provides data showing an increase in message- in one kidney tumor tissue. However, there is no evidence regarding whether or not PRO1268 polypeptide levels are also increased. Furthermore, as discussed in the previous Office Action (28 June 2005, pages 4 and 5), what is often seen is a *lack* of correlation between DNA expression and increased peptide levels (Pennica, et al, 1998, Proc. Natl. Acad. Sci., 95: 14717-14722). As discussed by Haynes et al (1998, Electrophoresis, 19: 1862-1871), polypeptide levels cannot be accurately predicted from mRNA levels, and that, according to the results presented, the ratio varies from zero to 50-fold (page 1863). The literature cautions researchers against drawing conclusions based on small changes in transcript expression levels between normal and normal kidney tissue. For example, Hu et al. (2003, Journal of Proteome Research 2: 405-412) analyzed 2286 genes that showed a greater than 1-fold difference in mean expression level between breast cancer samples and normal samples in a microarray (p. 408, middle of right column). Hu et al. discovered that, for genes displaying a 5-fold change or less in tumors compared to normal, there was no evidence of a correlation between altered gene expression and a known role in the disease. However, among genes with a 10-fold or more change in expression level, there was a strong and significant correlation between expression level and a published role in the disease (see discussion section).

The specification of the instant application does not complement the low (2-fold) PRO1268 expression data with any protein studies. The skilled artisan would not reasonably assume that PRO1268 polypeptide is overexpressed in one kidney tumor tissue versus normal kidney tissue based on the disclosure, without actually testing for PRO1268 polypeptide underexpression or overexpression.

Regarding Hu et al. (cited by the examiner in the previous Office Action), Applicant argues that Hu et al. does not conclusively show that it is more likely than not that the gene expression does not result in increased expression at the mRNA and polypeptide levels. Applicant contends that since Hu et al. only studied the statistical analysis of microarray data and not the gene expression data, their findings would not be directly applicable to the gene expression data. Applicants also state that Hu et al. manipulated various aspects of the input data. Applicants' arguments have been fully considered but are not found to be persuasive. The asserted utility for the claimed polypeptides is based on a sequence of presumptions. Firstly, since data were pooled and no statistics were presented, the instant disclosure does not reliably show fluorescence of PRO1268 within an experimental group. Secondly, it is presumed that increased mRNA production leads to increased protein production. Hu et al. is directly on point by showing that the second presumption is incorrect when designating proteins as diagnostic markers for cancer. Hu et al. (2003, Journal of Proteome Research 2:405-412) analyzed 2286 genes that showed a greater than 1-fold difference in mean expression level between breast cancer samples and normal samples in a microarray (p. 408, middle of right column) and discovered that, for genes displaying a 5-fold change or less in tumors compared to normal, there was no evidence of a correlation between altered gene expression and a known role in the

disease. However, among genes with a 10-fold or more change in expression level, there was a strong and significant correlation between expression level and a published role in the disease. The instant specification does not disclose that PRO1268 mRNA levels are expressed at 10-fold or higher levels compared with normal, matched tissue samples. Therefore, based on Hu et al., the skilled artisan would not reasonably expect that PRO1268 protein could be used as a cancer diagnostic. Regarding Applicant's criticism of Hu et al.'s statistical analysis, Applicants are holding Hu, et al to a higher standard than their own specification, which does not provide proper statistical analysis such as reproducibility, standard error rates, etc. When viewed with the evidence of record as a whole, there is no correlation between gene expression, mRNA levels and protein levels. In view of the totality of the evidence, including the Declarations submitted under 37 CFR 1.132 and the publications of record, the instant utility rejection is appropriate.

Applicants assert that the Patent Office has failed to meet its initial burden of proof that claims of Utility are not substantial or credible. They contend that the examiner's reasoning is based on a misrepresentation of the scientific data presented in the above cited references and application of an improper, heightened legal standard. Applicants state that the art indicates that, if a gene is amplified in a tissue, it is more likely than not that the encoded protein will be expressed at an elevated level.

Applicant's arguments have been fully considered but are not found to be persuasive. The truth or credibility of the assertion of utility has not been questioned. Rather, the rejection sets forth that the assertion of utility is not substantial. The preponderance of evidence supports this position. See Pennica et al. (cited in the previous Office Action) and Hu et al. (who

reviewed 2286 genes reported in the literature to be associated with breast cancer). These references, taken into consideration with the disclosure, indicate to the skilled artisan that it is more likely than not that PRO1268 polypeptide is not useful as a cancer diagnostic agent. Applicants discuss (Response, 29 September 2005, page 3 and throughout) points from case law in reference to the utility rejection, most of which the examiner agrees with. However, the fact patterns of the cases cited have little connection with utility/enablement as applied to the instant Application. Whatever the asserted specific utility might be - diagnosis of cancer, for example- it is **not** "more likely than not" (In re Oetiker, 1992, 977 F2d 1443, 1445, 24 USPQ2d) or true "to a reasonable probability" (Fujikawa v. Wattanasin, 1996, 93 F3d 1559, 39 USPQ2d 1895) since the increase in message was found in only one cancerous tissue.

Applicants indicate that the PRO1268 mRNA was increased in one kidney tumor tissue versus normal kidney tissue and showed a large increase in message, i.e., at least 2-fold expression. At pages 8-9 of the Response, Applicants argue that the expression of the nucleic acids encoding the claimed polypeptide is significant for the detection of kidney tumor and cite the Grimaldi Declaration. However, no substantially new arguments have been presented. These Declarations were previously considered and discussed by the Examiner in the Office Action of 28 June 2005. However, it is again noted that the PRO1268 gene or mRNA has *not* been associated with tumor formation or the development of cancer, nor has it been shown to be predictive of such. The specification merely demonstrates that the PRO1268 nucleic acid was increased in one cancer samples. No mutation or translocation of PRO1268 has been associated with any type of cancer. For these reasons, it is not clear that the reported expression is meaningful. In the absence of any of the above information, all that the specification has done is

present evidence that the mRNA encoding PRO1268 is amplified in one kidney tumor tissue and invites the artisan to determine the significance of this increase. One cannot determine from the data in the specification whether the observed "expression" of mRNA is a real measurement and due to an increase in transcription rates. It remains that, as evidenced by Pennica et al., the issue is simply not predictable, and the specification presents a mere invitation to experiment.

Therefore, based on the totality of the evidence, it is maintained that one skilled in the art would view the instant expression data as merely preliminary with regard to whether or not mRNA or protein levels of PRO1268 are specifically increased in kidney tumor. Further research would have to be done in order to determine if PRO1268 mRNA and protein are amplified and, if so, whether or not the expression is significant enough to reasonably confirm the usefulness of PRO1268 protein as a cancer marker. Thus, the claimed invention does not provide products or services in "currently available form" to the public, and the asserted utility is not substantial.

The fact remains that the instant specification does not disclose whether or not the PRO1268 gene or protein is reliably overexpressed in any one kidney tumor tissue. The skilled artisan must perform further research in order to reasonably confirm overexpression and specificity of positive fluorescence. The requirement for such further research indicates that the asserted utility of PRO1268 as a cancer diagnostic agent is not substantial. The specification does not disclose the expression levels of PRO1268 protein in any tissue samples; such would have to be determined through further research on the part of the skilled artisan. Thus, even the utility proposed regarding the usefulness of PRO1268 protein in the diagnosis of cancer is not

substantial. Finally, there is no disclosure regarding what treatment modality should be chosen by the clinician based on whether or not PRO1268 polypeptide is overexpressed. The determination of such constitutes further experimentation, indicating that the asserted utility is not substantial.

Applicants contend that the Haynes data (cited by Examiner in previous Office Action) confirm that there is a general trend between protein expression and transcript levels, which meets the "more likely than not standard" and shows that a positive correlation exists between mRNA and protein. Applicants also point out that Haynes is not relevant to the current application because Haynes did not compare mRNA expression levels and protein levels in the same yeast cells and thus the analysis by Haynes is not applicable to the present application.

Applicant's arguments have been fully considered but are not found to be persuasive. Haynes et al. clearly state "[p]rotein expression levels are not predictable from the mRNA expression levels" (pg 1863, top of left column) and "only the direct analysis of mature protein products can reveal their correct identities, their relevant state of modification and/or association and their amounts" (pg 1870, under concluding remarks).

Applicants cite Gygi, et al (1999, Mol. Cell. Biol., 19(3): 1720-1730) as evidence that mRNA and protein levels are highly correlated in mammalian tissues. However, the authors in that study concluded that mRNA levels are not predictive of protein levels. For example, they state: "We found that the correlation between mRNA and protein levels was insufficient to predict protein expression levels from quantitative mRNA data" (see Abstract). Likewise, in the Discussion, they summarized their data: "we speculate that there is no predictive correlation between steady-state levels of mRNA and those of protein in mammalian cells." It is true that

the overall measured correlation coefficient was 0.935. However, the authors themselves discount this result, stating: "This number is highly biased by a small number of genes with very large protein and message levels" (page 1726, second paragraph), and that for most genes the correlation coefficient is between -0.05 and 0.35 (see Figure 6).

Regardless of whether there is a correlation between mRNA and protein levels in a sample, the data presented in the instant Application do not show a meaningful positive response since the signal-to-noise ratio was small and only one kidney tumor tissue was positively stained or fluoresced.

Applicants conclude that one of skill in the art would reasonably expect in this instance, based on the expression data for the PRO1268 gene, that the PRO1268 polypeptide is concomitantly overexpressed. They argue that the PRO1268 polypeptides have utility in the diagnosis of cancer, and, based on such a utility, one of skill in the art would know exactly how to use the claimed polypeptides for diagnosis of cancer.

Applicant's arguments have been fully considered but are not found to be persuasive. The Examiner concedes that the specification teaches how to make PRO1268 polypeptide from the polynucleotide. However, the specification fails to provide a substantial asserted utility for the claimed PRO1268 polynucleotides (specifically, the specification fails to teach the skilled artisan how to use the claimed PRO1268 polynucleotides without undue experimentation). As discussed above, PRO1268 message was found to be slightly amplified in a sample of kidney tumor tissue compared to normal tissue. The literature reports that increased mRNA levels do not correlate with increased polypeptide levels in healthy tissue (see Haynes et al.) or normal

tissue (see Hu et al). In view of the totality of the evidence, the skilled artisan would not reasonably assume that PRO1268 polypeptide is overexpressed in a certain tissue based on the disclosure regarding gene expression, without actually testing for PRO1268 polypeptide overexpression. The requirement for such testing indicates that the asserted utility is not substantial, i.e., it is not in currently available form. Fourth, based on the disclosed data, the skilled artisan *also* would not presume that PRO1268 polypeptide is *not* overexpressed in certain tissues without actually testing for PRO1268 polypeptide levels. In view of such and the lack of guidance regarding how the physician would use information regarding PRO1268 polypeptide overexpression, or lack of overexpression, in categorizing a tumor and choosing a treatment modality, the asserted utility for PRO1268 polypeptide as a cancer diagnostic agent is not substantial. In view of the totality of the evidence, the rejections for lack of utility and enablement is proper.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after

the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no, however, event will the statutory period for reply expire Later than SIX MONTHS from the mailing date of this final action.

Advisory information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sandra Wegert whose telephone number is (571) 272-0895. The examiner can normally be reached Monday - Friday from 9:00 AM to 5:00 PM (Eastern Time). If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Brenda Brumback, can be reached at (571) 272-0961.

The fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

SLW
2 January 2006

JANE[illegible]RES
SUPER[illegible] EXAMINER